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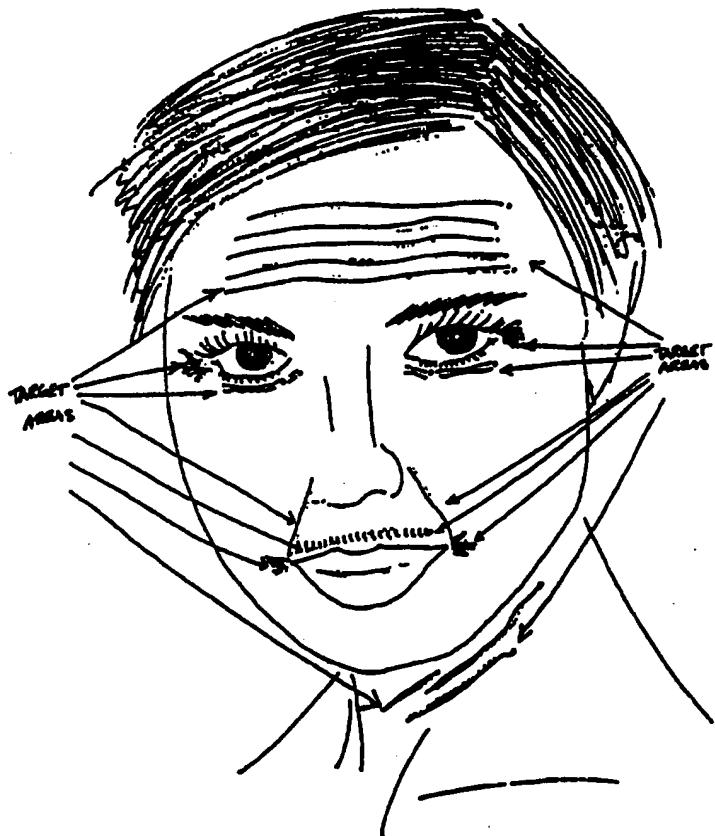
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(54) Title: SKIN CARE COMPOSITIONS AND METHODS

(57) Abstract

Skin care compositions and methods are provided for improving the appearance of skin affected by aging, photodamage and/or oxidative stress. Specifically, adhesive materials containing cosmetically active ingredients, e.g., one or more antioxidants such as Vitamins A, C and/or E, or moisturizers are applied to target areas including the frowline area of the forehead, the front of the neck, the crows-feet area near the eyes, the upper lip and the nasolabial area.



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## SKIN CARE COMPOSITIONS AND METHODS

### Field of the Invention

This invention relates to skin care compositions and methods for the improvement of the appearance of aging skin, in particular, to the improvement of wrinkling skin in target areas including but not limited to the areas outside and under the eyes, in the nasolabial area, the upper lip, the forehead, the neck and the hands.

### Background of the Invention

People in general are very concerned with maintaining youthful and attractive appearances. As populations age, it is anticipated there will be increasing markets for skin care products which can improve the appearance of aging skin and/or maintain attractive skin qualities. Treatments designed to prolong or promote youthful appearance include topical applications of cosmetic preparations, lotions and moisturizer, electrical stimulation, collagen injections and cosmetic surgery.

With aging, prolonged or repeated exposure to ultraviolet radiation and/or oxidative stress, the skin of the face often shows signs of damage resulting from such exposure. Aging or other damage to skin may be recognized by effects including wrinkling, yellowing, laxing, lines, spots, mottling and a leathery or dry appearance. At the histological level, skin damage, e.g., from photoaging, may be reflected in tangled, thickened, abnormal elastic fibers, decreased collagen and increased glycosaminoglycan content (Tanaka et al. (1993) *Arch. Dermatol. Res.* **285**:352-355). The aging process results in thinning and deterioration of the skin. There is a reduction in cells and in blood supply, and a flattening in the junction between the dermis and epidermis.

Ascorbic acid (Vitamin C), Vitamin A, tocopherol (Vitamin E) and β-carotene, which can at least in part be functionally characterized as antioxidants, are essential to the maintenance of a healthy and attractive skin appearance in humans. Vitamin K is also beneficial to maintaining attractive skin. Generally, these nutrients are obtained in the diet and/or in nutritional supplements. Other cosmetically beneficial components can be applied topically for improving skin appearance and quality; such components include moisturizers, including but not limited to polysaccharides and marine extracts.

The aforementioned antioxidants help to prevent damage to skin and/or body organs resulting from poor nutrition, physiological processes and exposure to environmental pollutants, certain drugs, alcohol, and ultraviolet (UV) radiation. Normal physiological processes, including aging, and exposure to deleterious agents can lead to the generation of free oxygen radicals, a

component of so-called oxidative stress. Oxidative stress leads to damage to cellular membranes, the genetic material and other cellular targets including connective tissue and collagen. Other sources of oxidative stress include heat, trauma, infection, hyperoxia, toxins and excessive exercise. Antioxidants can donate electrons without generating potentially harmful chain reactions and oxidation of cellular components, and thus provide protection from oxidative damage. A further problem, especially with aging skin is a decrease in blood circulation.

5 Ascorbic acid (Vitamin C) is known to stimulate and/or regulate collagen synthesis in human tissue. When collagen synthesis is stimulated in skin, a healthier and younger skin appearance results. Ascorbic acid can also help to prevent or minimize UV-induce lipid oxidation, thus providing 10 further benefits in maintaining or promoting attractive skin appearance. Further, ascorbic acid acts to inhibit melanin synthesis, which leads to skin discoloration during the aging process, and to inhibit histamine release from cellular membranes, which is associated with allergenic reactions, particularly among individuals with so-called "sensitive skin."

15 Ascorbic acid-containing compositions for topical application to the skin have been described (see, e.g., U.S. Patent No. 4,983,382, issued Jan. 8, 1991; Avon Products, Inc.). U.S. Patent No. 4,999,348, issued March 12, 1994, Estee Lauder, Inc., refers to cholesteric liquid crystal compositions for controlled release and enhanced penetration of biologically active materials such as Vitamin A to the skin. Vitamin A is said to make wrinkling in the skin less noticeable. U.S. Patent No. 5,238,965, issued August 24, 1993, Procter & Gamble Company, refers to regulating 20 wrinkling using topical applications of lipophosphatidic acid compositions. WO 94/00109 and WO 94/00098 (Lancaster Group AG), both incorporated by reference, refer to dermatological agents for increasing oxygen transport in the skin; these agents comprise phospholipids and oxygen-loaded fluorocarbons. U.S. Patent No. 5,296,500 (issued March 22, 1994, Proctor & Gamble Co.) claims methods for regulating wrinkles or atrophy of the skin using compositions comprising N-acetyl 25 cysteine, including compositions where one or more additional components (sunscreen, antioxidants, anti-inflammatory agents) are added. The present invention has the advantage over these conventional preparations in that absorption of Vitamin C or other cosmetically active ingredient into the skin can continue over an extended period of time without the extra effort or inconvenience of needing to actively apply another coat of a lotion, cream or the like.

30 Tocopherol (Vitamin E, with  $\alpha$ -tocopherol being the most potent) has effects in the skin including antioxidant activity, improved membrane stability, protection against UV radiation and nitrosamine formation, moisturizing action on dry skin and anti-inflammatory action. It is the antioxidant effect which is believed most important in protection from oxidative damage. Tocopherol has also been shown to play a role in maintaining the structural integrity of cell 35 membranes and connective tissue. Firmness, texture and/or tone are maintained by the integrity of the elastic fiber in the dermis and collagen in connective tissue. Vitamin E is also believed to

improve the hydration of the skin, and insufficiently hydrated skin is characterized by lines at relatively closer distance than in normal skin, irregular texture and a "scruffy" appearance.

It has been reported that only about 20-40% of oral vitamin E is absorbed, and it is not known what fraction of the absorbed vitamin E is available to the skin. Topically applied vitamin E, either in the alcohol or the acetate form, can be absorbed through the skin. When combined with ascorbyl palmitate which acts as an oxygen scavenger, tocopherol is particularly effective as an antioxidant to extend the shelf-life of natural products formulations such as perfumes, vitamins and herbal extracts.

$\beta$ -carotene within physiologically advantageous levels is also essential for skin development. An excess of  $\beta$ -carotene inhibits the keratinization of epithelial tissue, and a deficiency results in acne-like blackheads.  $\beta$ -carotene also acts to improve the skin's water barrier properties, and therefore  $\beta$ -carotene can be useful in treating seasonal and/or environmental problems (heat, dryness, air pollution). Provision of  $\beta$ -carotene to the skin will increase the amount of Vitamin A within the skin, and thereby impart beneficial effects on appearance of skin.

Other cosmetically active compositions, when topically applied to the skin, include marine extracts and moisturizers, for example, hyaluronic acid. Marine extracts, for example, those prepared from seaweed, are rich in minerals, amino acids, vitamins, and polysaccharides which are believed to function as moisturizing agents. Additional embodiments of a skin care patch can increase the oxygen supply to the skin, for example, using oxygen-loaded fluorocarbon compounds (as disclosed in WO 94/00109, WO 94/00098, for example) within the patch. Further embodiments include patches comprising cosmetically effective amounts of an active ingredient such as lysophosphatidic acid, an  $\alpha$ -hydroxyacid and N-acetyl cysteine.

Transdermal delivery of pharmaceutical compositions is well known. Such well-known pharmaceutical compositions include scopolamine for treatment of motion sickness, estrogen replacement therapy and nicotine for assistance in breaking tobacco habits. The present invention is believed to be the first application of transdermal delivery systems for skin care and the improvement of the appearance of aging, photodamaged or oxidatively stressed skin, especially for the improvement of the appearance of wrinkled skin.

#### Brief Description of the Drawings

Fig. 1 is a sketch of a typical aging human face with wrinkles under and in the outside corners of the eyes, the forehead, upper lip, the area from the outside bottom edges of the nose to the outside corners of the mouth (the nasolabial fold area) and the neck.

Fig. 2 illustrates a human face with the transdermal delivery device for application of cosmetically active compositions in place on the forehead.

Fig. 3 illustrates a human face with a pair of the transdermal delivery devices for application of cosmetically active compositions in place in the nasolabial fold area.

Fig. 4 illustrates a human face with the transdermal delivery device for application of cosmetically active compositions in place on the nasolabial fold area upper lip.

Fig. 5 illustrates a human face with a pair of the transdermal delivery devices for application of cosmetically active compositions in place at the outer corners of the eyes.

5 Fig. 6 illustrates a human with the transdermal delivery device for application of cosmetically active compositions in place on the neck.

Fig. 7A-7B illustrates a human hand with the transdermal delivery device (cross-hatched) for application of cosmetically active compositions in place on the back of the hand, with extensions on the backs of the fingers and thumb in Figure 7A and without finger extensions in Figure 7B.

10 Summary of the Invention

It is an object of this invention to provide cosmetic compositions and methods for improving the appearance of aging skin or skin damaged by overexposure to oxidative stress, sunlight or ultraviolet light and the like. With treatment, the appearance of the wrinkling of the skin becomes less apparent. Other outward indications of aging, photodamage or oxidative stress to the skin such as mottling, laxness, spots, dryness or leatheriness can also be lessened or slowed. The method of this invention is the percutaneous (or intradermal) delivery to the skin of cosmetically active compositions including antioxidants, for example, ascorbic acid, vitamin A, vitamin E, B-carotene or a combination thereof, via a transdermal delivery device. Other cosmetically active ingredients which can be incorporated into a transdermal (or intradermal) delivery device for sustained application to the skin include moisturizers (e.g. hyaluronic acid) and marine extracts from kelp and/or algae, essential fatty acids, collagen and lipids.

20 Preferably, the antioxidant is Vitamin C, from 50 to 1000 mg per square inch in an adhesive matrix. More preferably ascorbic acid is formulated with a cosmetically acceptable salt of ascorbic acid in proportions such that the pH of the combination in solution is about 4 to about 7, preferably, about 5 to about 6, most preferably about 5.5. Those salts include, but are not limited to, sodium ascorbate, potassium ascorbate and calcium ascorbate, preferably sodium ascorbate. Where sodium ascorbate is combined with ascorbic acid in the matrix, the preferred ratio is from about 1:20 to about 1:25 acid: salt, preferably about 1:22.

25 Preferably, the delivery device is adhered to the skin using a silicone pressure sensitive adhesive, but other adhesives are known to the art, including but not limited to, natural, isobutyl and butyl rubber compositions and acrylate-based adhesives and pressure sensitive adhesives. The configuration of the delivery device for the sustained delivery of cosmetically active ingredients to the skin can be adhesive matrix, liquid or solid state reservoir or polymer matrix; the preferred delivery device is the adhesive matrix type. In an adhesive matrix type patch, there is an impermeable backing, a matrix comprising the cosmetically active ingredient, optionally comprising a permeation enhancer and/or an anti-irritant, and a release liner.

In most transdermal delivery systems, thin, flexible occlusive films serve as protective backing substrate and release liner. For the present skin care applications, an occlusive protective backing substrate is preferred over a non-occlusive backing substrate. The materials used for liner and backing provide storage stability by keeping the active ingredients from migrating into or through the backing material and liner before use. The patches of the present invention desirably have the following tape properties: release or peel force < 50 g/cm; tack value > 50 g/cm; adhesion force 100-1200 g/cm; release force < 1 g/cm; preferably the adhesion force is about 50-300 g/cm and the shear force is about 14 kg/8.25cm<sup>2</sup>. Preferably, the adhesive is a medical grade silicone adhesive. The peel force required to remove the release liner from the patch should be sufficient to prevent inadvertent separation of the liner from the patch before use and low enough so that it can be readily removed by the intended user.

Where an acrylic adhesive is used, that adhesive is medical grade and rated between 0 and 2, preferably between 0 and 1 on the Draize Code Scale. On this scale a score of 0 means no erythema (reddening) and no edema (swelling when a test patch is applied to the skin and removed). The acrylic adhesive can optionally include a cross-linking agent.

Liquid and solid state reservoir transdermal delivery devices are configured so that the reservoir comprising the cosmetically active ingredients, enhancers and any other formulation ingredients is located between the backing material and the adhesive, and during use, formulation ingredients pass through the adhesive and then into the skin. Compatibility of various excipients and penetration enhancers with adhesives are well known to the art, and the skilled artisan can readily choose suitable concentrations and combinations of ingredients and adhesives.

A typical non-silicone polymer matrix transdermal delivery device has a rim of adhesive so that the penetration enhancer, cosmetically active ingredient(s) and other formulation ingredients are not fully in contact with the adhesive. In the preferred embodiment, the entire patch is adhesive and contains at least one cosmetically active ingredient. One surface is applied to the intended position on the face with gentle pressure to promote adhesion, after removal of a release liner. The other surface (away from the skin) is covered with a protective backing during storage, before use and during use.

Where desired, the skin care patches of the present invention optionally comprise formulation ingredients which either increase or decrease the release rates and/or absorption rates of the cosmetically active ingredients. Water soluble additives which increase release rate include ethylene glycol, glycerine, polyethylene glycols 200, 400, 600; polysorbate 80, lactose, gelatin, sucrose, sodium alginate, carboxymethyl cellulose, ammonium chloride, and polyvinylpyrrolidone. Lipid soluble additives which tend to increase release rate include cholesterol. Certain surfactants also have the effect of increasing release rate; these surfactants include sodium lauryl sulfate, dodecyltrimethylammonium chloride and azone. Release rates can be decreased by the addition of

compounds including such fillers as kaolin, Sephadex G-25 (high pressure liquid chromatography gel filtration resin) and silica.

The skin care patches of the present invention can optionally further include an irritant buffer such as sodium bicarbonate, which is incorporated at 1-10% by weight when present, or a stabilizing agent, such as propylgallate or sodium bisulfite.

Preferably, the skin care transdermal or intradermal delivery devices (patches) are shaped specifically for the target skin area to be treated. A generally rectangular with chevron patch is advantageously applied to the lower forehead area, an example of which is illustrated in Fig. 2. For application beneath and at the outer corners of the eye a generally kidney-shaped patch is used, and the shapes for the right and left sides are mirror images of one another. For the nasolabial fold area, the patch is shaped substantially like a boomerang, generally kidney-shaped. Skin care patches are also provided which fit the back of the hand, optionally with extensions down the fingers. Figures 2-7 illustrate human faces and hands with the aforementioned anatomically designed skin care patches in place.

#### 15 Detailed Description of the Invention

A transdermal or intradermal delivery device, known colloquially as a patch, is a unit which adheres to the skin of an individual, and allows for sustained release of an active ingredient into the skin, from which the active ingredient usually enters systemic circulation. Types of patches include liquid reservoir, solid state reservoir, polymer matrix, adhesive matrix and wet wick patches, depending on the configuration of the active ingredients and the patch materials. The active ingredients in an intradermal delivery device for improving the appearance of aging or photodamaged skin can include one or more of the following: alpha hydroxyacids, alpha ketoacids and polymeric hydroxyacids, moisturizers, collagen, marine extract and anti-oxidants including one or more of a tocopherol (Vitamin E),  $\beta$ -carotene, Vitamin A and Vitamin C (and/or cosmetically acceptable salts thereof), and are generically termed cosmetically active ingredients herein. A preferred tocopherol compound is  $\alpha$ -tocopherol. Additionally or alternatively, cosmetic benefits may be obtained by the use of skin care patches comprising molecules (e.g., fluorocarbons) capable of improving oxygen supply in skin tissue, as described, e.g., in WO 94/00098 and WO 94/00109.

Because of the beneficial effects of various cosmetically active ingredients, it has been a longstanding objective of skin care products to deliver effective concentrations of the active ingredients to the skin's tissue matrix (the dermal layers) via the most effective method possible to achieve maximal skin appearance benefits. Topical application of cosmetically active ingredients including but not limited to antioxidants, moisturizers and marine extracts via a transdermal delivery device has several advantages over topical application of a conventional formulation such as a lotion, creme or ointment in that with a patch, application is passive and continuous delivery of the active ingredient can be achieved for up to 24 hrs, or longer. Conventional topical application is limited by the amount of lotion, etc. which is administered, the amount of the active ingredient

which penetrates and the depth to which it penetrates, oxidation of the active ingredients before or during penetration and evaporative loss of solvents and/or active ingredients from lotions and the like. With a patch, evaporation is minimal, even when a non-occlusive patch is used.

Skin care patches can also include cosmetically active ingredients other than antioxidants; 5 for example, one or more of marine extracts, moisturizers and collagen, with or without a penetration enhancer, can be loaded in the reservoir, matrix or wet wick transdermal patch. Moisturizers can be one or more of hyaluronic acid, marine extract (of kelp and/or algae), fatty acids, lipids, and glycerides. Alpha hydroxyacids, alpha keto acids and polymeric hydroxyacids, for example, as described in U.S. Patent No. 5,091,171 (Yu and Van Scott), which is incorporated by reference herein, can be incorporated into the adhesive matrices of skin care patches to ameliorate 10 the unattractive effects of aging, photodamage or oxidative stress.

The active antioxidant ingredients for cosmetic patch compositions are present in a 15 cosmetically effective amount, preferably from about 1-1000 mg per patch. Ascorbic acid (and/or a cosmetically acceptable salt thereof), tocopherol, Vitamin A and  $\beta$ -carotene are preferred antioxidants. Taurine can also be used. Preferably, each active ingredient is present at about 75 mg per square inch.

In combination with one or more antioxidants (or other cosmetically active ingredients), 20 there are advantageously combined skin penetration-enhancing agents, i.e., agents which increase the penetration of the active ingredients into the skin which lead to improved skin appearance and at locations within the skin where the antioxidant effects of the active ingredients are beneficial in preventing or minimizing damage due to such agents as UV radiation, oxidative stress and aging in general. Generally, percutaneous absorption enhancers act by reducing the permeability or diffusion resistance of the stratum corneum, for example, by changing the hydration or by influencing the packing structure of the ordered lipids in the intercellular channels. Permeability 25 enhancers tend to be small polar molecules with outstanding solvent and hydrogen-bonding properties. Penetration is generally better where the stratum corneum is well hydrated. The skilled artisan knows how to choose a permeability enhancer with properties compatible with those of the adhesive and the active ingredients whose permeability into the skin is desired.

Examples of processes within the dermal layer affected by the application of antioxidants, 30 moisturizers and other cosmetically active ingredients can include, but are not limited to, collagen synthesis and reactions associated with oxidative stress.

The permeability enhancer is selected using parameters understood in the art including the appropriate solubility characteristic of the active ingredient in the enhancer, maximizing of the partitioning of the active ingredient into the skin, and enhanced percutaneous absorption, while not interfering with the requirements for the adhesive and its sticking properties.

Preferred penetration enhancing compounds (also called permeability enhancers) are those which are not toxic, not irritating to the skin and not allergenic. Exemplary penetration enhancing

compounds include but are not limited to vegetable oils such as soybean, sesame, palm, almond, peanut, olive and castor oils as described in WO 93/12744. Other permeability enhancing compounds include palmitate, alkanols (Friend et al. (1988) *J. Controlled Release* 7:243), dimethylsulfoxides (Scheuplein et al. (1971) *Physiol. Rev.* 51:702), urea (Feldman et al. (1974) *Arch. Dermatol.* 109:58), azone (Eurocapram, Nelson Research Corp., Stockton, CA) (Stoughton (1982) *Arch. Dermatol.* 118:474), fatty acids (Cooper (1984) *J. Pharm. Sci.* 73:1153), alkyl esters (Friend et al. (1984) *J. Controlled Release* 9:33), N,N-dialkyl-substituted amino acetates (Wong et al. (1989) *Pharm. Res.* 6:286), detergents and surfactants (Bettley et al. (1985) *Br. J. Dermatol.* 77:98), lecithins (Mahjour et al. (1990) *J. Controlled Release* 14:243), polyethylene glycol monolaurates (Iyer et al. (1985) Abstract 132nd Annual Meeting, APHA Acad. Phar. Sci. 15:81) glyceryl monolaurates (Cheng et al., U.S. Patent No. 4,746,515, issued 1988), pyrrolidone derivatives (Sasaki et al. (1991) *J. Pharm. Sci.* 80:533) and terpenes (Williams et al. (1991) *Pharm. Res.* 8:17). Only a limited number of these compounds are used in transdermal products, among them Miglyol 849 (propylene glycol diesters of caprylic and capric acids, Mahjour et al. (1993) *Int. J. Pharmaceutics* 95:161). Preferably, the permeability enhancing ingredient is present at a concentration of about 1-50% by weight, more preferably from about 1-20% by weight in an adhesive-active ingredient mixture. The penetration enhancer must be compatible with the active ingredients and with the polymeric material of the patch, as will readily be understood by the skilled artisan. For a discussion of permeation enhancers compatible with patch technology, see Pfister and Hsieh (1990) "Permeation Enhancers Compatible with Transdermal Drug Delivery Systems: Part I: Selection and Formulation Considerations and "Part II: System Design Considerations," *Pharmaceutical Technology*, September 1990 and October 1990, respectively.

A preferred matrix-type skin care patch contains a cosmetically effective amount of an antioxidant (Vitamin C or E or β-carotene), preferably Vitamin C (and/or a cosmetically acceptable salt), and preferably at a concentration of about 2-50% (about 75 mg per square inch), optionally with a penetration enhancer present at a concentration of about 1-10% by weight. The preferred adhesive is a medical grade silicon polymer adhesive.

The patch itself is preferably made of silicon, acrylate or polyisobutylene type polymeric material. Preferably the patch is made of a polymeric material which is chemically and biologically inert, non-toxic, non-irritating, non-sensitizing, non-allergenic and has adhesive properties which are easily manipulated. The patch material should further be flexible, with good cohesive strength (shear strength of > 5 kg/6.25 cm), suitable and easily controlled tack properties, low release force so that it can be readily removed from the liner backing and easily manipulated skin adhesion. The patch should have tack and adhesive properties which allow rapid adherence to the skin after minimal application of gentle hand pressure, and the matrix should rapidly mold itself closely with the contours of the target skin for best transfer of active ingredients. Adhesion properties can be determined using techniques well known to the art, for example using a digital probe tack tester

(e.g., Polyken, Testing Machines, Amityville, NY) and as described in Pfister et al., *Pharmaceutical Technology*, January 1992, pp. 42, 46. The desired adhesion of the silicone pressure sensitive adhesive is between about 50 and 300 g/cm, preferably 80-300 g/cm. If the adhesion is above this level, then the adhesive is too aggressive to the skin. If the adhesion is below this level, then the patch may fall off. One way of controlling the adhesion is by the amount of resin in the pressure sensitive adhesive. More resin may result in a higher adhesion. An impermeable film is bound to the surface of the patch destined to be away from the skin during use; a release liner is bound to the surface of the patch destined to be applied to the skin during use, and the release liner is removed prior to use. The impermeable film is not permeable to the active ingredient(s), but it may be occlusive, or more preferably, nonocclusive. The skilled artisan understands how to manipulate the adhesive composition in combination with the active ingredients so as to maintain desirable adhesive properties and effective delivery of the cosmetically active ingredient(s).

Adhesives, e.g., acrylic adhesives and pressure sensitive adhesives can be rated according to the Draize Dermal Scoring Code. A score of 0 means there is no erythema or edema after test application; 1 means barely perceptible reddening or swelling; 2 means well defined erythema or slight edema; 3 means moderate to severe erythema or moderate edema (raised 1mm); and 4 reflects severe erythema (beet redness) to slight eschar formation and severe edema (raised >1mm and extending beyond the area of exposure). Nontoxic adhesives with Draize Code Scores of 0-1 are deemed suitable for use on premature infants, and such medical adhesives can also be used in the skin care patches of the present invention without injuring or irritating the relatively delicate facial and neck target skin areas. Medical acrylate adhesives and/or medical acrylic pressure sensitive adhesives with Draize scores of 0-1 are well known and commercially available.

The acrylate-based matrix preferably contains medical acrylate adhesive, preferably pressure-sensitive adhesive, and active ingredient in a ratio of from about 40:60 to about 60:40, preferably about 50:50 by weight. It is understood that the incorporation of the cosmetically active ingredient into the adhesive may change the adhesion of the matrix composition relative to adhesive alone. Adjusting (increasing) the thickness of the matrix composition can compensate for some loss of adhesiveness.

The surface of the transdermal or intradermal delivery device which is away from the skin may be non-occlusive, i.e., permeable to air and/or water, or it may be occlusive, i.e., non-permeable to water vapor.

Pressure sensitive adhesives useful in transdermal and intradermal delivery devices include those silicone pressure sensitive adhesives comprising a mixture of a silicone resin and a silicone fluid or a condensed product of a silicone resin and a silicone fluid and an acrylic polyisobutylene (PIB); the pressure sensitive adhesive exhibiting suitable tackiness and adhesiveness for delivery of cosmetically active ingredients to sensitive or delicate skin.

The silicone resin may be further described as being a soluble, hydroxyl-functional organopolysiloxane resin comprising  $R_3SiO_{1/2}$  siloxane units and  $SiO_{4/2}$ , wherein R is selected from a monovalent radical selected from the group consisting of hydrocarbon and halogenated hydrocarbon radicals having 1 to 20 carbon atoms. In the  $R_3SiO_{1/2}$  and  $SiO_{4/2}$  nomenclature the 1/2 and 4/2 represent the number of half bonds on the molecule shown. For example, in  $R_3SiO_{1/2}$  there is one (1) 1/2 bond which is on the oxygen. The other half of that bond being bonded to some other atom. Another way of describing this group is by  $R_3SiO-$  or by



Similarly,  $SiO_{4/2}$  has four (4) 1/2 bonds in the molecule shown. The other half of each bond being bonded to some other molecule. Again, other way of describing this group is by



By the term "soluble" it is meant that the organopolysiloxane can be dissolved substantially completely, in either a hydrocarbon liquid such as benzene, toluene, xylene, heptane and the like 20 or in a silicone liquid such as cyclic or linear polydiorganosiloxanes. Preferably the resin is soluble in the silicone fluid.

In the formula for the silicone resin, R denotes a monovalent radical selected from the group consisting of hydrocarbon and halogenated hydrocarbon radicals, preferably having less than 20 carbon atoms, and most preferably having from 1 to 10 carbon atoms. Examples of suitable R 25 radicals include alkyl radicals, such as methyl, ethyl, propyl, pentyl, octyl, undecyl, octadecyl and others; cycloaliphatic radicals, such as cyclohexyl; aryl radicals such as phenyl, tolyl, xylyl, benzyl, alpha-methyl styryl, 2-phenylethyl and others; alkenyl radicals such as vinyl; and chlorinated hydrocarbon radicals such as 3-chloropropyl, dichlorophenyl and others.

To enhance the solubility of the silicone resin in the silicone fluid, it is desirable to select the predominant organic radicals of the former to match the predominant organic radicals of the latter. Preferably, at least one-third, and more preferably substantially all, R radicals in the formula for the 30 silicone resin are methyl radicals. Examples of preferred  $R_3SiO_{1/2}$  siloxane units include  $Me_3SiO_{1/2}$  and  $PhMe_2SiO_{1/2}$  and  $Ph_2MeSiO_{1/2}$  where Me denotes methyl and Ph denotes phenyl.

It is preferred that the ratio of  $R_3SiO_{1/2}$  siloxane units to  $SiO_{4/2}$  units has a molar ratio of 0.5 35 to 1.2, respectively. It is further preferred that the mole ratio of the total  $R_3SiO_{1/2}$  siloxane units to  $SiO_{4/2}$  units be between 0.6 and 0.8.

The silicone resin can be prepared by well known methods. It is preferably prepared by the silica hydrosol capping process of U.S. Patent No. 2,67,182 (Daudt et al.) as modified by U.S. Patent No. 3,627,851 (Brady) and U.S. Patent No. 3,772,247 (Flannigan); each patent being

incorporated herein by reference to teach how to prepare soluble organopolysiloxanes which are useful in transdermal delivery devices. The resulting resin can be used in the pressure sensitive adhesive composition without further modification or it can be capped with trialkylsilyl groups to reduce the silanol content. This can be accomplished by well known methods, such as reacting the resin with a compound such as trimethylchlorosilane or hexamethyldisilazane.

5 The silicone fluid is preferably a hydroxyl-terminated diorganopolysiloxane polymer. The repeat units of the silicone fluid are  $R_2SiO_{2/2}$  siloxy units wherein R is independently selected from the same hydrocarbon and halogenated radicals as defined above for the silicone resin. The silicone fluid can be comprised of a single polymer or copolymer or it can be a mixture of two or more such polymers. The silicone fluid can be a liquid or gum at 25°C. It is preferred that at least 50%, and preferably at least 85%, of the organic radicals along the chain of the silicone fluid are methyl radicals, which can be distributed in any manner in the silicone fluid. Further, the silicone fluid can comprise up to about 10 mole percent of siloxane branching sites, provided it meets the above viscosity requirements.

10 15 The silicone resin is employed in amount from about 40 to 70 parts by weight in the silicone pressure sensitive adhesive, and the silicone fluid is employed from about 30 to about 60 parts by weight, wherein the total parts of the silicone resin and the silicone fluid are 100 parts. It is usually preferred that the silicone resin be employed from about 50 to 60 parts by weight, and correspondingly, the silicone fluid be employed from about 40 to 50 parts by weight, wherein the total parts by weight equals 100.

20 The silicone resin and silicone fluid may be blended together to produce the pressure sensitive adhesive, or they may be condensed together to produce the pressure sensitive adhesive. Methods of condensing together the silicone resin and silicone fluid are well known in the art.

25 One class of pressure sensitive adhesives employed in transdermal delivery devices consists of a mixture of a trimethylsilyl-endblocked polysilicate resin such as a silicone resin consisting of a benzene-soluble resinous copolymer containing silicon-bonded hydroxyl radicals and consisting essentially of triorganosiloxy units of the formula  $R^1_3SiO_{1/2}$  and tetrafunctional siloxy units of the formula  $SiO_{4/2}$  in a ratio of about 0.6 to 0.9 triorganosiloxy units for each tetrafunctional siloxy unit present in the copolymer, wherein  $R^1$  is a monovalent organic radical independently selected from the group consisting of hydrocarbon radicals of from 1 to 6 carbon atoms, and (ii) a silanol-endcapped polydiorganosiloxane fluid such as a polydimethylsiloxane fluid. U.S. Patent No. 2,736,721 to Dexter et al. and U.S. Patent No. 2,814,601 to Currie et al. are hereby incorporated by reference to teach of such or similar pressure sensitive adhesive compositions.

30 35 Another class of suitable pressure sensitive adhesives used in transdermal delivery devices are the pressure sensitive adhesives in U.S. Patent No. 2,857,356 (Goodwin, Jr.), which is hereby incorporated by reference, or pressure sensitive adhesives similar to those in Goodwin. U.S. Patent No. 2,857,356 discloses a silicone pressure sensitive adhesive which consists of a mixture of

ingredients comprising (i) a cohydrolysis product of a trialkyl hydrolyzable silane and alkyl silicate, wherein the cohydrolysis product contains a plurality of silicon-bonded hydroxy groups, and (ii) linear, high viscosity organopolysiloxane fluid containing silicon-bonded hydroxy groups.

5 The silicone resin (i) and the silicone fluid (ii) may optionally be condensed together according to a procedure such as described in Canadian Patent 711,756 to Pail, which patent is hereby incorporated by reference. In such a condensation reaction, the silicone resin (i) and silicone fluid (ii) are mixed together in the presence of a catalytic amount of a silanol condensation catalyst, and then the silicone resin (i) and the silicone fluid (ii) are condensed, for example, by heating under reflux conditions for 1 to 20 hours. Examples of silanol condensation catalyst are primary, 10 secondary and tertiary amines, carboxylic acids of these amines and quaternary ammonium salts.

Another class of suitable pressure sensitive adhesives for use in transdermal or intradermal delivery devices are those compositions described in U.S. Patent No. 4,591,622 and 4,584,355 to Blizzard et al., U.S. Patent No. 4,585,836 (Homan et al.), and U.S. Patent No. 4,655,767 (Woodard et al.), hereby incorporated by reference. Generally, these pressure sensitive adhesives consist of 15 a blend of (i) a silicone resin and (ii) a silicone fluid which are chemically treated to reduce the silicone-bonded hydroxyl content of the blend. These adhesives may optionally be condensed, as described previously, prior to the chemical treatment.

Silicone pressure sensitive adhesives useful in transdermal or intradermal delivery devices 20 should not be confused with silicone rubbers, which are not useful in these applications. Silicone pressure sensitive adhesives are usually fillerless or contain low amounts (less than 5%) of fillers. By contrast, silicone rubbers typically contain about 15 to 35% filler. Fillers are generally not required in high quantities in silicone pressure sensitive adhesives, because high quantities often cause the silicone pressure sensitive adhesives to lose tack and adhesiveness and to increase in dynamic viscosity, making it more difficult to apply a coating of the silicone pressure sensitive adhesive. 25

Small amounts of additional ingredients, such as pigments, stabilizers, fillers and others, 30 may be added to the silicone pressure sensitive adhesives as long as they do not materially alter the requirements of the desired composition. If the silicone pressure sensitive adhesive compositions contain a filler, it is desired that the filler be present in an amount of no greater than 5 weight percent based on the total weight of the silicone resin and silicone fluid.

Reference may be made to U.S. Patent Nos. 4,840,796 (Sweet et al.), 4,951,657 (Pfister et al.), 4,655,767 (Woodard et al.) and/or 5,232,702 (Pfister et al.), all incorporated by reference herein, for discussion of transdermal delivery devices and pressure-sensitive adhesive compositions for use in such devices.

35 The ascorbic acid-containing skin care delivery device is specifically exemplified in Example 2. Other anti-oxidant compounds (e.g., tocopherol or Vitamin A) can be substituted in the formulation for the ascorbic acid.

The nature of the adhesive on the side of the patch applied to the skin is important. It is preferably chemically and biologically inert, not toxic, irritating or sensitizing, moisture resistant, and it should have minimal cold flow for easy removal, it should be flexible, suitable tack for quick sticking but easily removed and restuck when adjustments are necessary during application, and have low release force for easy removal of the liner. The adhesive should be non-irritating to the skin, and the adhesiveness should be sufficient to adhere the patch to the skin for at least from about 7 to about 12 hrs, but the patch should not adhere to the skin so tightly that the force required to remove it results in skin damage due to pulling or stretching of the skin. The skilled artisan knows how to choose cohesive strength, creep resistance, end-use tape properties, including tack, peel force and skin adhesion, commensurate with the application to and removal from delicate facial skin.

Preferred rheological properties for the adhesive-active ingredient matrix described in Example 2.3, at a frequency of 0.01 and a temperature of 30°C, are as follows:

G' (storage, or elastic, modulus) about  $1 \times 10^8$  to about  $1 \times 10^9$ , preferably about  $6 \times 10^8$ ;  
 15 G" (loss or fluid modulus) about  $3 \times 10^6$  -  $1.4 \times 10^7$ , preferably about  $7-9 \times 10^6$ ; and  
 N' (intrinsic viscosity) of about  $4 \times 10^8$  -  $4 \times 10^9$ , preferably about  $7 \times 10^8$  -  $2 \times 10^9$ .

TABLE 1  
 Rheological Properties Measured at Different Frequencies (composition of Example 2.3)

	<u>Frequency</u>	<u>G'</u>	<u>G"</u>	<u>N'</u>
20	0.01	$5.5 \times 10^8$	$8.9 \times 10^6$	$1.1 \times 10^9$
	0.1	$2.3 \times 10^7$	$2.1 \times 10^7$	$3.1 \times 10^8$
	1.0	$5.4 \times 10^7$	$3.7 \times 10^7$	$8.6 \times 10^7$
25	10	$1.0 \times 10^8$	$6.4 \times 10^7$	$1.2 \times 10^8$
	100	$1.8 \times 10^6$	$7.2 \times 10^7$	$1.0 \times 10^8$

Rheological properties were determined using a Rheometrics Viscoelastic Tester (Rheometrics, Piscataway, NJ) at an angular shear frequency from 0.01 to 100 rads/s at 30°C using the parallel plate method of testing.

Tape properties of the above adhesive-active ingredient mixture (see also Example 2.3) are given in Table 2:

TABLE 2  
 Tape Properties of the Composition of Example 2.3

	<u>Thickness (mils)</u>	<u>Release force (g/cm)</u>	<u>Adhesion (g/cm)</u>	<u>Shear kg/6.25cm<sup>2</sup></u>
35	0.5	1	4	6
	1.2	2	9	5
	2	1	3	3
	2.6	2	5	2
	4.7	1	7	<1

Preferred rheometric properties for the adhesive-active ingredient matrix described in Example 2.3 at 35.4°C (which approximates skin temperature) are given in Table 3:

TABLE 3  
Frequency Sweep 35.4°C

No.	Temp °C	Frequency rad/s	G' dyn/cm.sq.	G" dyn/cm.sq.	N° P
10	35.4	1.0 x 10 <sup>-2</sup>	3.8 x 10 <sup>6</sup>	7.1 x 10 <sup>6</sup>	8.1 x 10 <sup>8</sup>
	35.4	2.1 x 10 <sup>-2</sup>	6.5 x 10 <sup>6</sup>	1.0 x 10 <sup>7</sup>	5.6 x 10 <sup>8</sup>
	35.4	4.6 x 10 <sup>-2</sup>	1.0 x 10 <sup>7</sup>	1.4 x 10 <sup>7</sup>	3.7 x 10 <sup>8</sup>
	35.4	1.0 x 10 <sup>-1</sup>	1.5 x 10 <sup>7</sup>	1.9 x 10 <sup>7</sup>	2.4 x 10 <sup>8</sup>
	35.4	2.2 x 10 <sup>-1</sup>	2.2 x 10 <sup>7</sup>	2.4 x 10 <sup>7</sup>	1.5 x 10 <sup>8</sup>
	35.4	4.6 x 10 <sup>-1</sup>	3.2 x 10 <sup>7</sup>	3.0 x 10 <sup>7</sup>	9.4 x 10 <sup>7</sup>
	35.4	1.0	4.3 x 10 <sup>7</sup>	3.7 x 10 <sup>7</sup>	5.6 x 10 <sup>7</sup>
	35.4	2.2	5.6 x 10 <sup>7</sup>	4.4 x 10 <sup>7</sup>	3.3 x 10 <sup>7</sup>
	35.4	4.6	7.2 x 10 <sup>7</sup>	5.1 x 10 <sup>7</sup>	1.9 x 10 <sup>7</sup>
	35.4	1 x 10 <sup>1</sup>	9.0 x 10 <sup>7</sup>	5.9 x 10 <sup>7</sup>	1.1 x 10 <sup>7</sup>
	35.4	2.2 x 10 <sup>1</sup>	1.1 x 10 <sup>8</sup>	6.7 x 10 <sup>7</sup>	5.9 x 10 <sup>6</sup>
	35.4	4.6 x 10 <sup>1</sup>	1.3 x 10 <sup>8</sup>	7.5 x 10 <sup>7</sup>	3.3 x 10 <sup>6</sup>
	35.4	1.0 x 10 <sup>2</sup>	1.6 x 10 <sup>8</sup>	8.3 x 10 <sup>7</sup>	1.8 x 10 <sup>6</sup>

These properties were determined using a Rheometrics Viscoelastic Tester (Rheometrics, Piscataway, NJ) at an angular shear frequency from 0.01 to 100 rads/s at 35.4°C (which approximates skin temperature) using the parallel plate method and frequency sweep mode of testing. The parallel plate had a radius of 4.000, a gap of 1.52, 8 mm diameter and .5% strain.

The preferred thickness range for this adhesive-vitamin C composition is 3 to 5 mils, and tape properties of release <5 g/cm, adhesiveness 1-50 g/cm, preferably 8-10 g/cm, and shear from 3-12 kg/6.25cm<sup>2</sup>, preferably 4-6 kg/6.25cm<sup>2</sup>. Although, with the test samples, the matrix material did not completely transfer from the release liner or the stainless steel plates, the samples did appear to be suitable for skin use, with no apparent residue remaining on the facial skin of test volunteers.

The resin-to-polymer ratio affects the tape properties of the formulation. Generally, an increase in relative resin content increases cross-linking within the matrix, reduces tack, increases adhesion and cohesion strength, and increases the force required to remove the release liner. Lower tack values are correlated with a slight increase in the ratio of viscous components of the modulus to the elastic components of the modulus. Generally, silicone resin levels of 45-70% give useful adhesive properties for pressure sensitive adhesives; for the present skin care application, 62-64% (by weight) resin content is preferred. On formulations which may depart from the desired rheological and adhesive properties, the skilled worker can readily modify the composition to achieve the desired properties using art-known principles and this disclosure without the expense of undue experimentation.

Although ascorbic acid matrix-type patches are effective for ameliorating the appearance of wrinkled skin, for example, wrinkled facial skin, there may be some irritation to the treated skin if the matrix does not contain a material which provides some buffering action or some partial

neutralization of the acidity of the ascorbic acid when it dissolves into the skin. It is preferred that the pH of the ascorbic acid matrix composition is between about 4 and about 7, more preferably from pH about 4 to about 6, and most preferably, about pH 5.5, which is the pH of most human skin. This pH can be achieved by combining the ascorbic acid with an irritant buffer such as sodium bicarbonate, but the disadvantage is that buffer is not an active ingredient. It is desirable to use a non-irritating, non-toxic, freely soluble salt of ascorbic acid, including but not limited to, sodium ascorbate, potassium ascorbate and calcium ascorbate. Where sodium ascorbate is used in combination with ascorbic acid, the ratio (by weight) of ascorbic acid to sodium ascorbate should be from about 1:20 to about 1:25, preferably about 1:22. It is understood that when cations other than sodium are used, the ratio must be adjusted according to the dissociation constants in solution and other properties of the ascorbate salt. Potassium ascorbate and calcium ascorbate are useful in combination with ascorbic acid in the present formulations, with appropriate modifications in ratio to achieve the desired solution pH, as readily apparent to the ordinary skilled artisan. Alternatively a solution of ascorbic acid can be adjusted in pH to the desired range using an alkali solution such as NaOH or KOH, among others, and then dried so that the ascorbate and cations can be prepared as a dry powder for use in the present cosmetically active transdermal delivery devices.

It is understood that for the present application the ascorbate salt will be non-toxic and not irritating and that it will be freely soluble in an aqueous environment. For the present purpose, these ascorbate compositions are termed cosmetically acceptable ascorbate salts. These include potassium, sodium, and calcium salts.

It is also understood that other dermatologically acceptable compounds can be used to raise the solution pH of the matrix composition comprising ascorbic acid. Such compounds are non-toxic and non-irritating to the skin, and include, but are not limited to, sodium acid phosphate, sodium borate, sodium citrate and sodium acid tartrate. It is noted that these compounds do not individually provide any cosmetic benefit.

For the present cosmetic application, the patches are specifically sized and shaped according to the target area. Preferably, the ends or edges of the patches are to be rounded, rather than sharp angles or corners. For the forehead, where use of the patches of the present invention are used to ameliorate or prevent the appearance of "frown lines" on the lower forehead, the patch is to be in the shape of a shallow chevron (see Fig. 2). The width of the patch is from about 5 to about 6 inches, and the height of the patch is from about 1.0 inch to about 1.75 inches, with the angle of the curved chevron being from about 90° degrees.

For the nasolabial area, the patch is generally boomerang-shaped (or an elongated kidney shape) which follows the outline of the wrinkle line falling between the nose and the corners of the mouth (see Fig. 3). The angle of the arms of the "boomerang" is from about 20° to about 30° off horizontal, the width of the patch from about 1/2 inch to about 5/8 inch, and the length of the patch about 2 inches.

For improving the appearance of wrinkled skin, age spots, mottling, etc., on the upper lip, a skin care patch is applied to the upper lip (See Fig. 4). Preferably, the cosmetic patch for this application has a shape which is characterized as a narrow rectangle which is slightly curved, with dimensions of about 5/8 inch in width and about 2 1/2 inches long, where the length is understood to be the dimension extending along the upper lip and the width is the dimension which extends from the lip toward the nose.

For the area at the outside corners of the eyes, the cosmetic patch is preferably an elongated kidney shape, with the patch width being from about 1/4 inch to about 1/2 inch and the length being about 1 3/4 inch (see Fig. 5).

For application to the neck, the transdermal device for the percutaneous delivery of cosmetic compositions as described above is illustrated in Fig. 6. This patch is generally rectangular in shape, but slightly curved, preferably with rounded corners, and the dimensions are about 5-6 inches by 2-3 inches.

For application for the back of the hand, the cosmetic patch is shaped as illustrated in Fig. 7A and 7B. This patch is generally square (about 2.5 - 3 inches), with rounded corners (Figure 7B). Optionally there can be five extensions to cover the backs of the fingers and thumb (Figure 7A).

The patches of desired shape can be produced from a larger sheet, with release liner, of adhesive material containing the cosmetically active ingredients in an adhesive matrix and/or any permeability enhancers and/or anti-irritants, by knife edge (cutting), gravure (printing) or other processes including extrusion or the active ingredient/permeability enhancer may be sprayed onto a backing material. Preferably, the active ingredients are mixed with the adhesive before application to the backing material.

The following examples are provided for illustrative purposes, and they are not intended to limit the scope of the invention as claimed herein. Any variations in the exemplified compositions and methods which occur to the skilled artisan are intended to fall within the scope of the present invention.

Example 1.      Silicone Pressure Sensitive Adhesive (PSA)

Preparation

A silicone pressure sensitive adhesive is prepared by condensing at 115 to 120°C, in the presence of 0.025 parts anhydrous ammonia, 66 parts of a 70 wt% xylene solution of a siloxane resin copolymer consisting essentially of  $(\text{CH}_3)_2\text{SiO}_{1.2}$  units and  $\text{SiO}_{4/2}$  units in a molar ratio of approximately 0.75:1 and containing approximately 2.7 weight percent hydroxyl based on solids as determined by FTIR (ASTM E-168), 28 parts of a hydroxyl-terminated polydimethylsiloxane having a viscosity of about 13,500 cP (mPa·s) at 25°C and 6 parts of xylene. Following the condensation reaction, the mixture was heated to 140°C for 1 hour to remove any excess ammonia. This silicone pressure-sensitive adhesive was found to have an adhesion of 268 g/cm at a thickness of 1-2 mils on a mylar backing.

Example 2. Ascorbic Acid-Silicone PSA Preparations

Three formulations have been prepared containing 50/50 (weight/weight) adhesive and ascorbic acid. The formulations are described below:

Example 2.1

5 A silicone pressure sensitive adhesive is prepared by condensing at 115 to 120°C, in the presence of 0.025 parts anhydrous ammonia, 67 parts of a 70 wt% xylene solution of a siloxane resin copolymer consisting essentially of  $(CH_3)_3SiO_{1/2}$  units and  $SiO_{4/2}$  units in a molar ratio of approximately 0.75:1 and containing approximately 2.7 weight percent hydroxyl based on solids as determined by FTIR (ASTM E-168), 31 parts of a hydroxyl terminated polydimethylsiloxane having a viscosity of about 13,500 cP (mP·s) at 25°C and 2 parts of xylene. Following the condensation reaction, the mixture was heated to 140°C for 1 hour to remove any excess ammonia.

10 The silicone adhesive mass was then mixed with an equal weight of ascorbic acid (ultrafine powder, Hoffman-LaRoche) for 17 minutes using a Lee stainless steel tilt kettle with a built-in 15 Eppinbach high shear mixer.

15 To produce adhesive laminates, the adhesive solutions are coated onto fluoropolymer coated release liner, SCOTCH PAK 1022 Release Liner (SCOTCHPAK, trade mark of 3M Company, St. Paul, MN) using a motorized adhesive coater (model no. 33782-6, RK Print-Coat Instruments, Ltd., Litlington, Royston, Herts, U.K.) and a smooth coating bar (Dow Corning Corp., Midland, MI) at a speed of 165 inches/minute to yield an approximately 1.8 mil ( $\pm$  0.2 mil) dry adhesive thickness and allowed to air dry overnight to allow evaporation of solvents. A sheet of heat sealable polyester film laminate (SCOTCHPAK 1220, trademark of 3M Company, St. Paul, MN) is then transfer-coated 20 and smoothed using a laminating roller (Laminating Rubber-covered Steel Roller, 3.25 in diameter x 1.75 in weighing about 4.5 lb, U.S. Testing Co., Hoboken, NJ) and eliminating air entrapment. 25 This preparation is then treated with a 4.5 lb, 1.8" wide rubber-coated roller (Pressure Sensitive Tape Council, Glenview, IL) to insure complete contact of the three layers. The resulting laminates contain a dry adhesive layer approximately 3-5 mil in thickness. This silicone pressure-sensitive adhesive/Vitamin C composition was found to have an adhesion of 136 g/cm at 1-2 mils on a mylar 30 backing. When this patch was applied to the skin or a surface, some adhesive remained on the skin when the patch was removed. However, it is believed that this will result in a suitable composition if a primer is used on the mylar backing.

Example 2.2

35 A silicone pressure sensitive adhesive is prepared by condensing at 115 to 120°C, in the presence of 0.01 parts anhydrous ammonia, 61 parts of a 70 wt% xylene solution of a siloxane resin copolymer consisting essentially of  $(CH_3)_3SiO_{1/2}$  units and  $SiO_{4/2}$  units in a molar ratio of approximately 0.75:1 and containing approximately 2.7 weight percent hydroxyl based on solids as determined by FTIR (ASTM E-168), 32 parts of a hydroxyl-terminated polydimethylsiloxane

having a viscosity of about 13,500 cP (mP·s) at 25°C and 7 parts of xylene. Following the condensation reaction the mixture was heated to 140°C. for 1 hour to remove any excess ammonia. Equal weights of ascorbic acid and adhesive were mixed as above, and then laminated to films as described above.

- 5 This silicone pressure-sensitive adhesive/Vitamin C preparation was found to have an adhesion of 99 g/cm at 1-2 mils on a mylar backing. No residue was left on the skin of test volunteers.

Example 2.3

- 10 A silicone pressure adhesive is prepared by condensing at 115 to 120°C, in the presence of 0.01 parts anhydrous ammonia, 63 parts of a 70% xylene solution (w/w) of a siloxane resin copolymer consisting essentially of  $(\text{CH}_3)_2\text{SiO}_x$  units and  $\text{SiO}_{4/2}$  units in a molar ratio of approximately 0.75:1 and containing approximately 2.7 weight percent hydroxyl based on solids as determined by FTIR (ASTM EI-68), 37 parts of a hydroxyl-terminated polydimethylsiloxane having a viscosity of about 13,500 cP (mP·s) at 25°C and 7 parts of xylene. Following the condensation reaction the mixture was heated to 140°C. for 1 hour to remove any excess ammonia. Equal weights of ascorbic acid and adhesive were mixed as above, and then laminated to films as described above.

15 This silicone pressure-sensitive adhesive/Vitamin C preparation was found to have an adhesion of 1-500 g/cm at 1-2 mils thickness on a mylar backing.

Example 3.

50 parts (as dry weight) of medical grade acrylic pressure sensitive adhesive (Draize scale score 0-1), dissolved in ethyl acetate and toluene, is mixed with 50 parts of (ascorbic acid and sodium ascorbate, both as dry powders, in a 1:22 (wt/wt) ratio) to form the cosmetically effective adhesive matrix. It is then cured at 250°F.

This adhesive matrix material is coated onto release liner (4.6 mil thickness of coating) and backing substrate laminate is applied as described hereinabove.

When tested on a human volunteer, this transdermal patch had suitable adhesive properties and suitable score on the Dermal Scoring Code (between 0 and 1). Moreover, this patch ameliorated the appearance of wrinkling near the outer corners of the eye of a man 45 years old.

**What is claimed is:**

1. A transdermal or intradermal delivery device for topical application of a cosmetic preparation, said device comprising a backing substrate, a matrix containing at least one active ingredient for improving the appearance and/or feel of the skin, and an adhesive suitable for facial skin use, said matrix being atop said backing substrate, and a release liner contacted on said matrix, wherein said delivery device has a shape adapted for a target area selected from the group consisting of the upper lip, the nasolabial fold area, the lower forehead, the front portion of the neck, the outer corners of the eyes, underneath the eyes and the back of the hands.
1. 2. The delivery device of claim 1 wherein said active ingredient is at least one of ascorbic acid or a cosmetically acceptable salt thereof, tocopherol and  $\beta$ -carotene.
1. 3. The delivery device of claim 1 further comprising a permeability enhancing agent suitable for facial skin use selected from the group consisting of palmitic acid, and isopropyl palmitate.
1. 4. The delivery device of claim 3 wherein said permeabilizing agent is isopropyl palmitate.
1. 5. The delivery device of claim 2 wherein said adhesive suitable for facial skin use is a pressure sensitive adhesive.
1. 6. The delivery device of claim 2 wherein said adhesive suitable for facial skin use is a pressure sensitive silicon adhesive.
1. 7. The delivery device of claim 5 wherein said adhesive suitable for facial skin use is a pressure sensitive acrylic adhesive.
1. 8. The delivery device of claim 2 wherein said active ingredient is at least one of ascorbic acid and a cosmetically acceptable salt thereof.
1. 9. The delivery device of claim 8 wherein said active ingredient is at a concentration of from 50 to 1000 milligrams per square inch.
1. 10. The delivery device of claim 9 wherein said cosmetically acceptable ascorbate salt is one sodium ascorbate, potassium ascorbate and calcium ascorbate.
1. 11. The delivery device of claim 10 wherein ascorbic acid and sodium ascorbate are in a ratio (weight: weight) of from about 1:20 to about 1:25.
1. 12. The delivery device of claim 10 wherein ascorbic acid and sodium ascorbate are in a ratio (weight: weight) of about 1:22.
1. 13. The delivery device of claim 8 wherein said ascorbic acid and said cosmetically acceptable salt thereof are present in proportions such that in solution a pH value of from about pH 4 to about pH 7 is achieved.
1. 14. The delivery device of claim 13 wherein said ascorbic acid and said cosmetically acceptable salt thereof are present in proportions such that in solution a pH value of from about pH 4 to about pH 6.

- 1        15. The delivery device of claim 14 wherein said ascorbic acid and said cosmetically acceptable salt thereof are present in proportions such that in solution a pH value of from about pH 5 to about pH 6.
- 1        16. The delivery device of claim 2 further comprising sodium bicarbonate at a concentration of from 1 to 10% by weight in the matrix.
- 1        17. The delivery device of claim 1 wherein the shape adapted for application to the upper lip is that of a narrow and slightly curved rectangle, about 0.625 inches in width and about 2.5 inches long and wherein the corners are rounded.
- 1        18. The delivery device of claim 1 wherein the shape adapted for application to the front of the neck is a slightly curved rectangle with rounded corners, between 5 and 6 inches in length and between 2 and 3 inches in width.
- 1        19. The delivery device of claim 1 wherein the shape adapted for application to the nasolabial fold area is an elongated kidney shape, about 2 inches in length and between 0.5 and 0.625 inches in width.
- 1        20. The delivery device of claim 1 wherein the shape adapted for application to the outer corners of the eyes is an elongated kidney shape, about 1.75 inches in length and between 0.25 and 0.5 inches in width.
- 1        21. The delivery device of claim 1 wherein the shape adapted for application to the lower forehead is a slightly curved rectangle, about 5 to 6 inches in length and between 1 and 1.75 inches in width, said rectangle having rounded corners and said rectangular further comprising a generally chevron shape at one edge of the length.
- 1        22. A method for improving the appearance of aging, photodamaged or oxidatively stressed skin, said method comprising the step of applying the transdermal or intradermal delivery device of claim 1 to at least one facial or hand target area.

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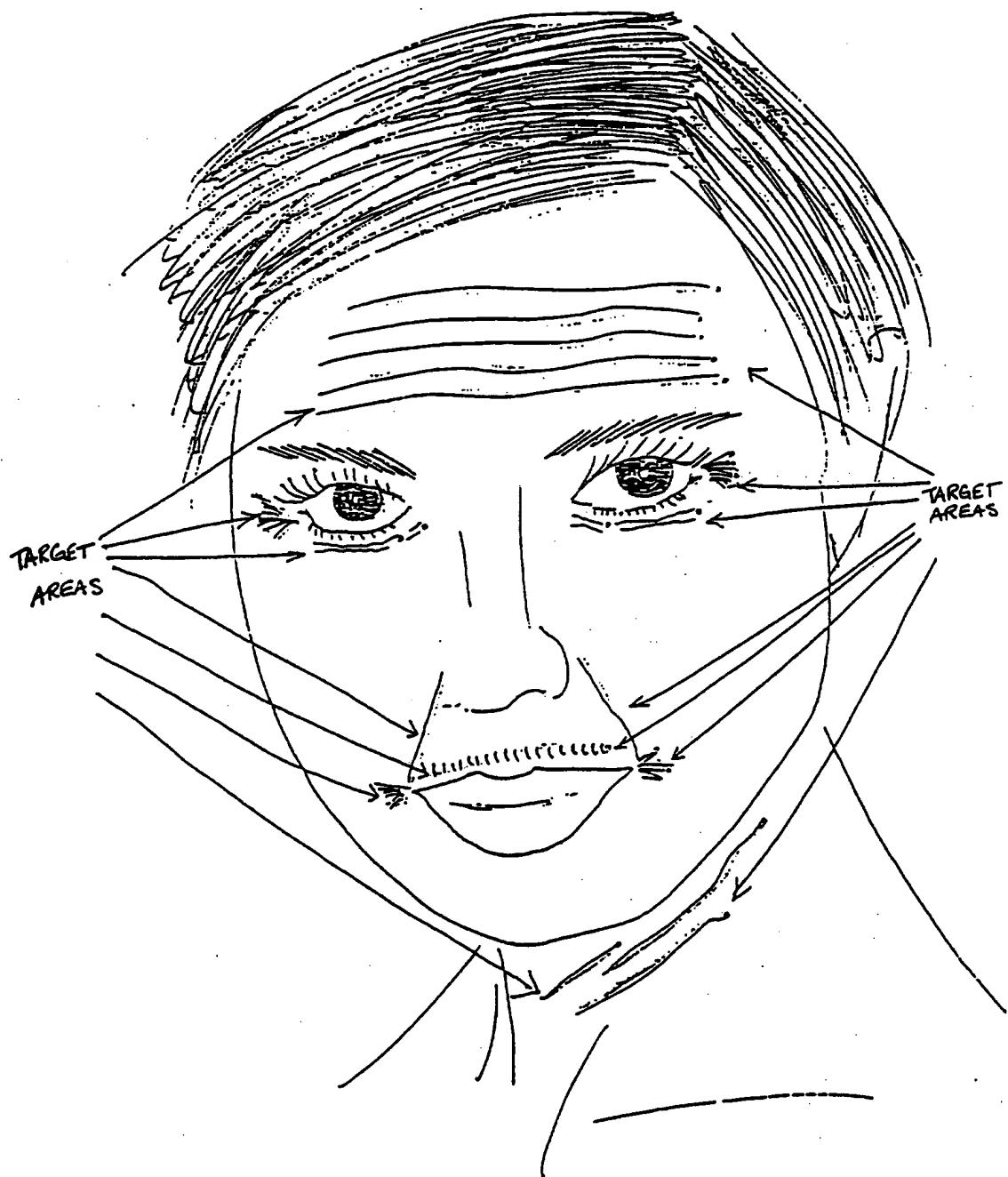
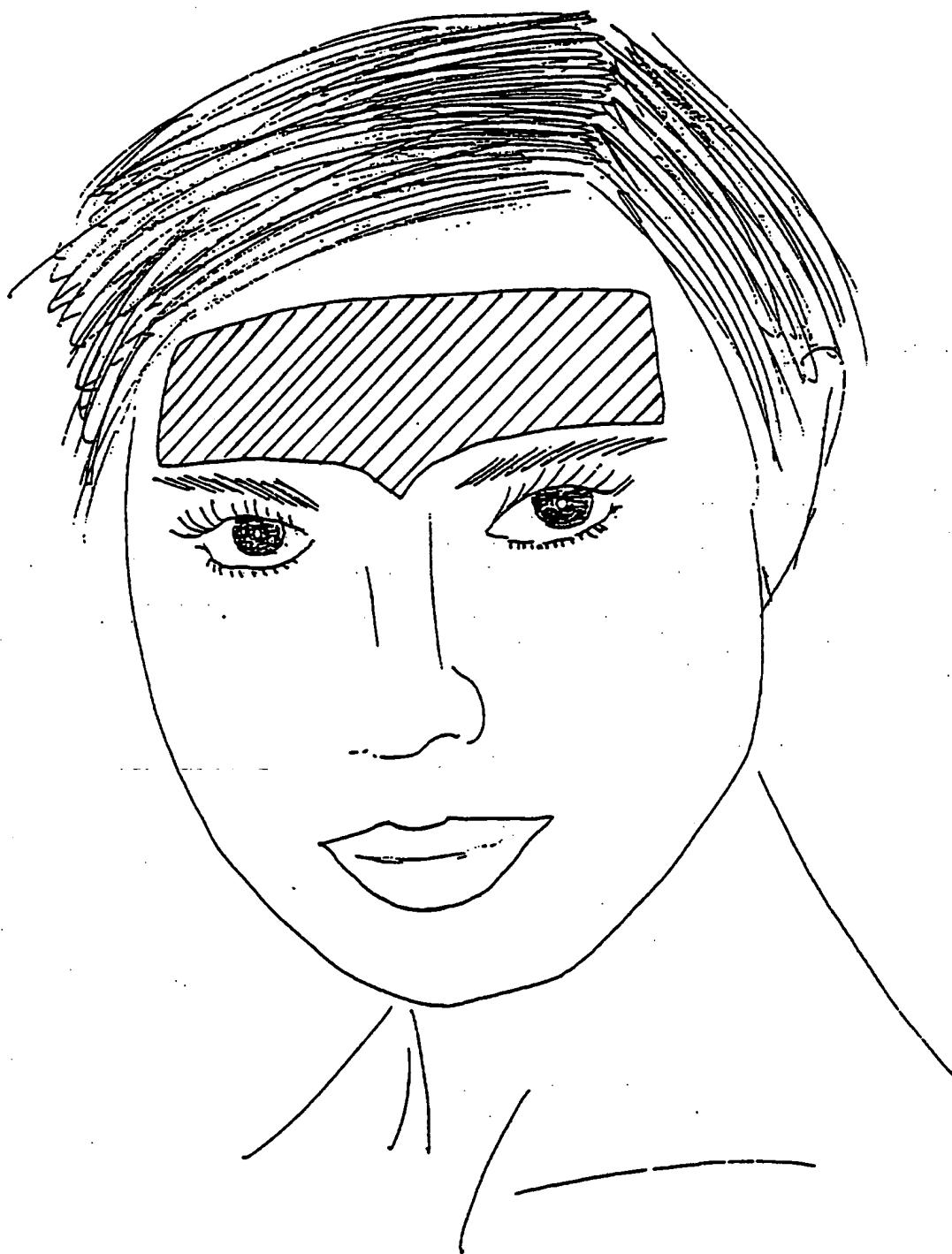


FIGURE 1

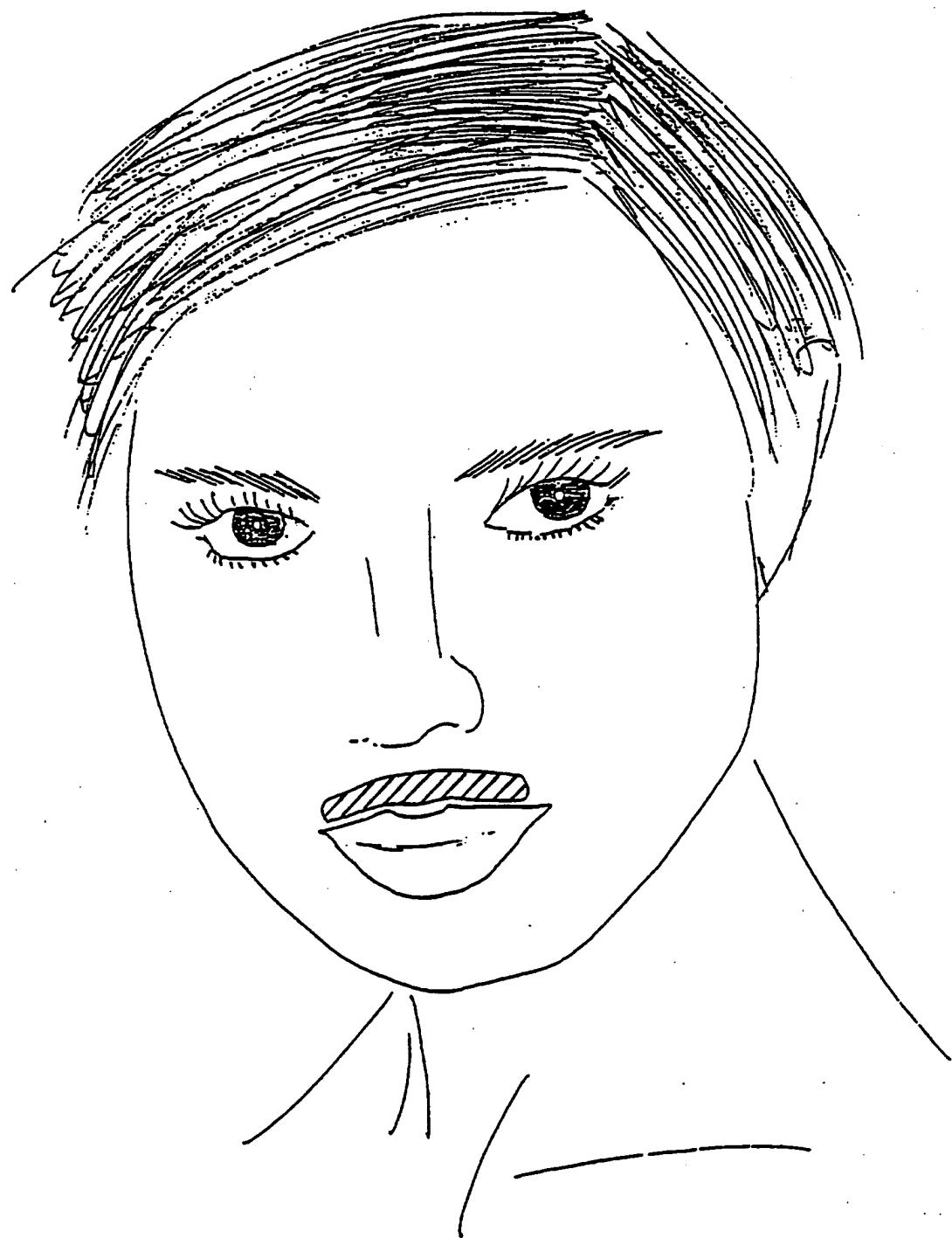


**FIGURE 2**

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FIGURE 3

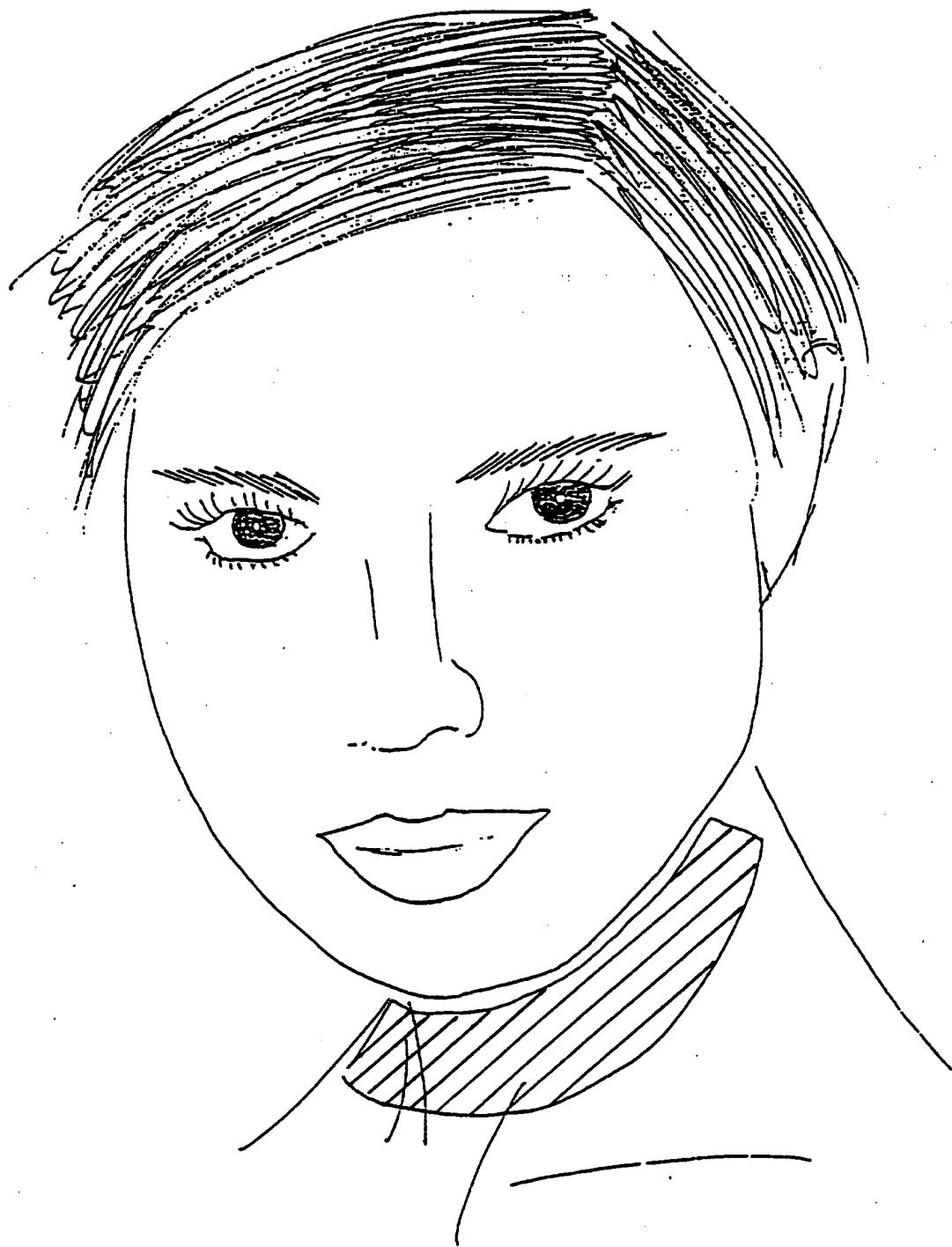


**FIGURE 4**

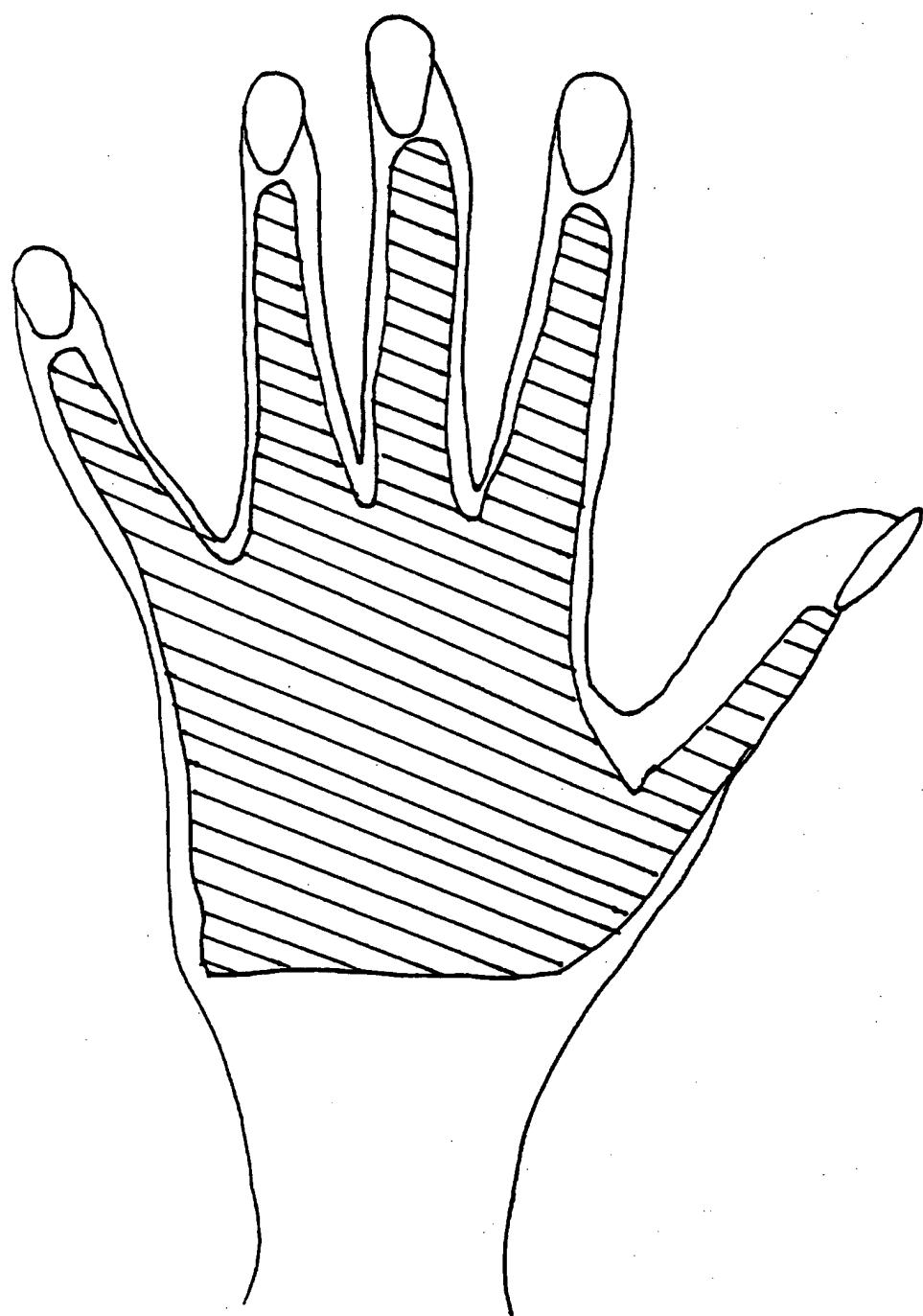


**FIGURE 5**

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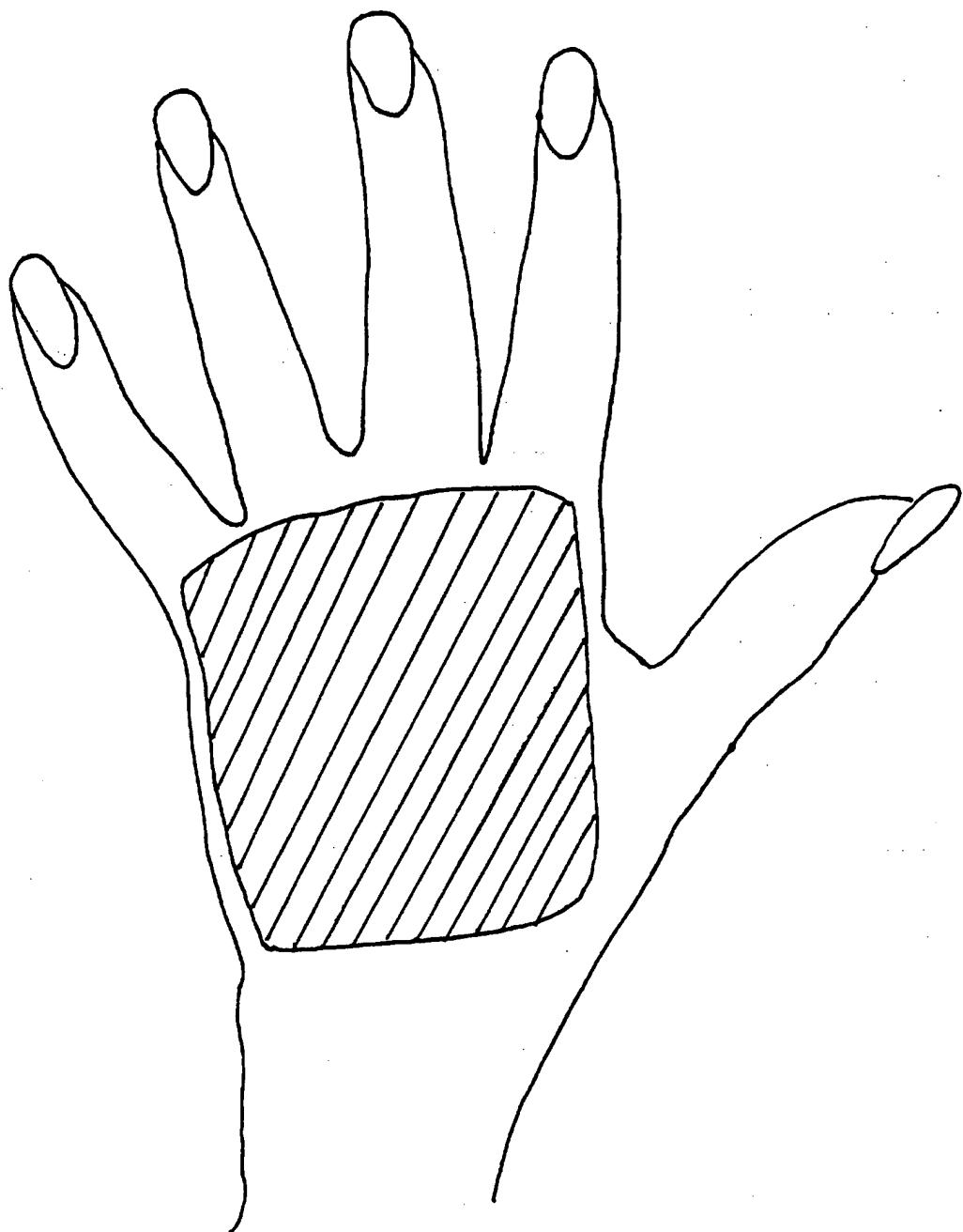


**FIGURE 6**



**FIGURE 7A**

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**FIGURE 7B**

## INTERNATIONAL SEARCH REPORT

International Application No PCT/US 95/14682
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A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K7/00 A61K7/48
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According to International Patent Classification (IPC) or to both national classification and IPC
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B. FIELDS SEARCHED
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Minimum documentation searched (classification system followed by classification symbols)
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IPC 6 A61K
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 265 086 (PACIFIC CHEM CO LTD) 22 September 1993 see page 11, paragraph 3-4; figure 2 ---	1,2,8, 10,22
X	EP,A,0 410 921 (AGUILERA FRANCO MARIA) 30 January 1991 see the whole document ---	1,22
A	DE,A,21 65 549 (FRUEH KARL) 5 July 1973 see the whole document ---	1
A	EP,A,0 063 875 (MAX FACTOR & CO) 3 November 1982 see page 5, line 20-25; claim 1; figures 1-4 ---	1 -/-

Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search  25 March 1996	Date of mailing of the international search report  10.04.96
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A	US,A,3 499 446 (TSUNEIZUMI YOSOJI ET AL) 10 March 1970 see the whole document ---	1,2
A	US,A,4 983 382 (WILMOTT JAMES M ET AL) 8 January 1991 cited in the application see the whole document ---	2,8
A	WO,A,94 15614 (AGIS IND 1983 LIMITED ;GODWIN EDGAR JAMES (GB)) 21 July 1994 see page 3-4; claims 1-4 ---	3,4
A	US,A,5 232 702 (PFISTER WILLIAM R ET AL) 3 August 1993 cited in the application see the whole document -----	5,6

1

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/14682

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-2265086	22-09-93	CN-A-	1076110	15-09-93
		JP-A-	7258060	09-10-95
EP-A-0410921	30-01-91	NONE		
DE-A-2165549	05-07-73	NONE		
EP-A-0063875	03-11-82	AU-B-	8216682	21-10-82
		GB-A-	2100980	12-01-83
US-A-3499446	10-03-70	NONE		
US-A-4983382	08-01-91	CA-A-	1325774	04-01-94
		JP-A-	1254609	11-10-89
WO-A-9415614	21-07-94	AU-B-	5711894	15-08-94
		CA-A-	2152907	21-07-94
		EP-A-	0677126	18-10-95
US-A-5232702	03-08-93	DE-D-	69204236	28-09-95
		DE-T-	69204236	21-03-96
		EP-A-	0524776	27-01-93
		JP-A-	5194201	03-08-93

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